Cortical pattern separation and item-specific memory encoding

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Highlights:

- We examined cortical pattern separation and completion during episodic encoding
- Parametric similarity analyses assessed perceptual and conceptual dimensions
- Mnemonic discrimination of lures was associated with hippocampal encoding activity
- PFC and occipital pattern separation regions also predicted accurate recognition
- This is consistent with a role of cortical pattern separation in successful encoding

Abstract

Pattern separation and pattern completion are fundamental brain processes thought to be critical for episodic memory encoding and retrieval, and for discrimination between similar memories. These processes are best understood in the hippocampus, but are proposed to occur throughout the brain, in particular in sensory regions. Cortical, as well as hippocampal, pattern separation may therefore support formation of event-unique memory traces. Using fMRI, we investigated cortical pattern separation and pattern completion and their relationship to encoding activity predicting subsequent item-specific compared to gist memory. During scanning, participants viewed images of novel objects, repeated objects, and objects which were both perceptually and conceptually similar to previously presented images, while performing a size judgement task. In a later surprise recognition test, they judged whether test items were 'same' 'similar' or 'new' relative to studied items. Activity consistent with pattern separation – responses to similar items as if novel – was observed in bilateral occipito-temporal cortex. Activity consistent with pattern completion – responses to similar items as if repeated – was observed in left prefrontal cortex and hippocampus. Curve fitting analysis further revealed that graded responses to change in image conceptual and perceptual similarity in bilateral prefrontal and right parietal regions met specific computational predictions for pattern separation for one or both of these similarity dimensions. Functional overlap between encoding activity predicting

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subsequent item-specific recognition and pattern separation activity was also observed in left occipital cortex and bilateral inferior frontal cortex. The findings suggest that extrahippocampal regions including sensory and prefrontal cortex contribute to pattern separation and pattern completion of visual input, consistent with the proposal that cortical pattern separation contributes to formation of item-specific memory traces, facilitating accurate recognition memory.

1. Introduction

Sensory information from a changing environment is continuously processed by the brain, often resulting in substantial overlap between incoming representations and traces already stored in long-term memory. In order to avoid interference, incoming episodes must therefore be assigned unique neural representations. In the hippocampus, this is thought to be achieved by pattern separation - the orthogonalisation of incoming relative to existing representations. Conversely, overlapping input is used at retrieval as a cue to drive reinstatement of existing traces via pattern completion, increasing overlap between incoming and existing representations (Marr, 1971; McNaughton and Morris, 1987; O'Reilly and McClelland, 1994). Although pattern separation is by definition an encoding process, and pattern completion a retrieval process, either or both can be elicited by a single event, whether novel or previously encountered (Hunsaker and Kesner, 2013). Efficient pattern separation at encoding is thought to contribute to later *mnemonic discrimination* between events with similar representations, while false recognition of similar events can result from inefficient pattern separation or dominance of pattern completion at encoding (Sahay et al., 2011; Stark et al., 2013; Wilson et al., 2006). However the precise mechanisms by which pattern separation and completion at encoding contribute to memory outcomes remain unknown, and it remains to be established whether and how neocortex complements the central role of the hippocampus in these computations. The present study investigated cortical pattern separation and completion, and asked whether regions showing these responses were also engaged during encoding leading to later item-specific memory.

Within the hippocampus, computational, electrophysiological and lesion evidence has implicated the dentate gyrus (DG) in pattern separation, and subfields CA3 and CA1 in pattern separation or completion, depending on the degree of overlap between incoming and existing representations (Gilbert et al., 2001; Guzowski et al., 2004; Leutgeb et al., 2007; Rolls, 2007; Vazdarjanova and Guzowski, 2004). High-resolution functional magnetic resonance imaging (fMRI) evidence from humans is consistent with these findings. Typically, these studies have examined responses to novel images of common objects, repetitions of these images, and images of perceptually and conceptually similar objects. By examining neural responses to similar images within regions showing differential activity between novel and repeated images, it is assumed that equivalent activity between similar and novel items is consistent with pattern separation, i.e., similar images are processed as if novel, whereas equivalent activity to similar items and repetitions is consistent with

pattern completion, i.e., similar items are processed as if repeated. Examining regions showing repetition suppression (Henson and Rugg, 2003), such investigations have reported activity consistent with pattern separation in a region spanning DG/CA3, and pattern completion activity in CA1 and elsewhere in the medial temporal lobe (MTL) (Bakker et al., 2008; Lacy et al., 2011). Although pattern separation and completion investigations have focussed on the role of the hippocampus, networks throughout the brain are thought to perform similar functions, including sensory cortex (Aimone et al., 2011; Gilbert and Kesner, 2003). Rodent electrophysiological recordings have demonstrated pattern separation of odour cues in the olfactory bulb, and pattern completion in piriform cortex (Barnes et al., 2008; Wilson, 2009), but these functions in regions outside the MTL have received little attention in studies in humans.

A number of fMR adaptation (fMRA) studies are also relevant to pattern separation and completion processes. These have assessed the information represented in specific regions by measuring stimulus-specific repetition suppression. Repetition suppression to exact repetitions but not perceptually and conceptually similar images has been reported in visual cortical regions including fusiform and lateral occipital cortex (LOC) (Chouinard et al., 2008; Koutstaal et al., 2001). Such responses resemble pattern separation in that similar items elicit a response which is distinct from that of repetitions. Repetition suppression to similar images which differ perceptually from previously viewed items has also been observed in other occipito-temporal regions and in left inferior frontal gyrus (LIFG) (Chouinard et al., 2008; Fairhall et al., 2011; Horner and Henson, 2011), resembling pattern completion. Such findings together suggest that cortical regions contribute to the degree to which visual inputs are coded as perceptually and semantically similar or distinct. However, evidence for pattern separation or completion from these studies is incomplete. Some studies have reported repetition suppression for repeated relative to both novel and similar items within the same anatomical region without showing that these responses actually overlap (Bakker et al., 2008; Kumaran and Maguire, 2009). Similarly, it has not yet been demonstrated that the regions showing repetition suppression to similar items also show attenuated activity to repetitions, as expected for pattern completion. One fMRA study however demonstrated occipito-temporal responses more clearly consistent with pattern separation. Kim et al. (2009) reported release from repetition suppression in bilateral LOC and fusiform in response to images which differed in shape but not basic-level concept relative to previous images. LOC activity also did not differ between conceptually similar and conceptually novel images equated in shape similarity with previously viewed images. Results were interpreted as sensitivity of LOC to change in shape information, but can also be interpreted from a pattern separation perspective, i.e., reduced activity for repetitions relative to both novel and similar images, but activity for novel and similar items did not differ, providing the most direct evidence to date of responses consistent with pattern separation in visual cortex.

Although the fMRA findings are suggestive of cortical pattern separation and completion, these processes are computationally defined in terms of their responses to parametrically varied input

similarity (e.g., Treves and Rolls, 1992; Vazdarjanova and Guzowski, 2004). Therefore, examination of neural responses to graded change in input, i.e., to stimuli of varying similarity relative to previously presented items, can provide further support for their presence (Hunsaker and Kesner, 2013; Kumaran and Maguire, 2009). Pattern separation is defined as reduction in overlap of output representations from a region relative to the degree of overlap of input representations received by the region (Rolls, 1996; Treves and Rolls, 1992). The resulting changes in output in response to increasing input similarity can therefore be approximated by a power function with decreasing slope, i.e., a large difference in activity occurs between repeated and the most similar items (Fig. 1A; Motley and Kirwan, 2012). In contrast, pattern completion *increases* the representational overlap at output relative to input representations (O'Reilly and McClelland, 1994), approximated by a power function with increasing slope, i.e., very slight differences in activity occur between repeated and similar items, with only highly dissimilar items processed as if novel (Fig. 1; Vazdarjanova and Guzowski, 2004). In regions showing repetition enhancement, the functions are the same but their direction is inverted (Fig. 1B). A linear function represents the case where overlap is equal between input and output representations, i.e., neither pattern separation nor completion occurs (Guzowski et al., 2004; Yassa and Stark, 2011). 'Input' and 'output' here refer to neural representations, and in line with other authors we approximate their similarity by that between items (Motley and Kirwan, 2012; Yassa et al., 2011). fMRI responses consistent with these predictions have been demonstrated in hippocampus in response to items of varied 'mnemonic similarity' (defining input similarity indirectly as the probability of successful mnemonic discrimination in a separate sample; Lacy et al., 2011), or varied viewing angle relative to previous images (Motley and Kirwan, 2012).

There has been little exploration in humans of the proposal that pattern separation at encoding contributes to later mnemonic discrimination (Kirwan and Stark, 2007; Wilson et al., 2006). In memory tasks incorporating similar lures at test as well as novel and studied items, successful mnemonic discrimination entails correct rejection of lures (as 'similar' or 'new') as well as the ability to recognise studied items, and lure false recognition reflects failed mnemonic discrimination. Consistent with a role of pattern separation in mnemonic discrimination, in rats, lesions to DG, strongly linked to pattern separation (e.g., Leutgeb et al., 2007), result in mnemonic discrimination deficits (Goodrich-Hunsaker et al., 2008); and in humans, associations have been demonstrated between both hyperactivation in CA3/DG and reduced perforant path integrity and poorer lure discrimination performance (Kirwan et al., 2012; Yassa et al., 2010). Kirwan and Stark (2007) reported that hippocampal (CA1, DG/CA3) but not other MTL regions showed encoding-related activity which differentiated between later mnemonic discrimination outcomes (lure correct rejection, lure false recognition, hits). They did not however examine the relation between this encoding activity and pattern separation. Efficient pattern separation at encoding is thought also to facilitate recognition of studied items as 'old' (Norman and O'Reilly, 2003; Yassa and Stark, 2011). Conversely, inefficient pattern separation at encoding and/or emphasis of overlap between current and existing

< Figure 1 about here >

representations via pattern completion is assumed to contribute to later false recognition of similar lures (Norman, 2010; Schacter et al., 1998; Yassa and Reagh, 2013).

Other theoretical accounts suggest that true and false recognition differ in terms of encoding and retrieval of item-specific information. According to Fuzzy Trace Theory, gist traces are coarse, acontextual representations of semantic information which are distinct from but encoded in parallel with item-specific representations of precise surface form (Brainerd and Reyna, 1990; 2002). It is suggested that false recognition of items overlapping in gist with studied items can result from emphasis on gist processing at encoding, leading to increased strength of gist relative to item-specific traces, and consequent reliance on gist at retrieval (Brainerd and Reyna, 2002). On this account, true recognition of studied items can be supported by gist information alone, but is often associated with intact item-specific memory in healthy, young adults (Gutchess and Schacter, 2012). In a recognition test with an explicit requirement to respond 'similar' to lures, memory for gist in the absence of item-specific memory may result in *partial recognition,* i.e., incorrectly judging studied items as 'similar' (Garoff et al., 2005). Successful mnemonic discrimination of a similar lure from its previously studied item is however thought to require intact item-specific memory as well as post-retrieval processing (Brainerd et al., 2003). Several fMRI studies have shown differences in encoding activity according to whether later memory is item-specific or gist-based. Activity in LIFG (Garoff et al., 2005; Kim and Cabeza, 2007; Kubota et al., 2006) and left superior temporal gyrus (Baym and Gonsalves, 2010) has been found to predict subsequent false recognition of images and visually presented words which are semantically similar to studied items, relative to subsequent forgetting. The assumption that this reflects semantic gist processing is consistent with behavioural studies showing that emphasis on semantic processing at encoding contributes to greater likelihood of false memory (Koutstaal and Schacter, 1997; Roediger and McDermott, 1995). However, contrasts of subsequent false recognition with forgetting provide limited information about what is unique to encoding supporting mnemonic discrimination. The same studies have found that encoding predicting true recognition engages visual cortex, e.g. bilateral fusiform gyri, inferior temporal cortex and LOC (Baym and Gonsalves, 2010; Garoff et al., 2005; Kim and Cabeza, 2007), suggesting additional perceptual processing may aid in formation of item-specific memory. These regions associated with encoding predicting true and false recognition are similar to those which in the fMRA studies discussed above were associated with sensitivity and invariance to perceptual change, respectively (Fairhall et al., 2011; Kim et al., 2009; Koutstaal et al., 2001). A small number of studies (Cheng and Rugg, 2010; Geng et al., 2007; Urbach et al., 2005) have also reported differences in electroencephalographic event-related potentials during encoding of words according to whether semantically similar lures are later mnemonically discriminated or falsely recognised, consistent with suggestions that different encoding processes contribute to these outcomes.

The present study had three main aims. First, we sought evidence for cortical activity consistent with pattern separation and/or completion during incidental encoding of images of novel objects, repetitions, and perceptually and conceptually similar objects (Bakker et al., 2008). We also assessed whether neural responses to images of graded perceptual and conceptual similarity relative to previously viewed images, defined by independent subjective ratings, met computational definitions for pattern separation and completion within repetition sensitive regions. Second, we examined the neural bases of encoding predicting recognition outcomes proposed to rely on item-specific memory (mnemonic discrimination of lures), gist-based memory (partial recognition of studied items, false recognition of lures) or both (true recognition). The recognition test employed studied, novel and lure images and participants made 'same', 'similar' or 'new' judgements (Garoff et al., 2005; Koutstaal et al., 1999). This task is thought to place greater demands on pattern separation than dichotomous old/new recognition (Stark et al., 2013), and supports direct comparisons between successful and unsuccessful lure mnemonic discrimination (Yassa et al., 2011). Finally, we assessed whether the same regions engaged in pattern separation or completion were also associated with item-specific or gist encoding.

Based on previous fMRA studies, it was predicted that bilateral inferior frontal cortex (Koutstaal et al., 2001) and occipito-temporal regions including bilateral LOC and fusiform would demonstrate pattern separation (Fairhall et al., 2011; Koutstaal et al., 2001), and would also be engaged in item-specific encoding (Kim and Cabeza, 2007). Encoding predicting gist memory was expected to engage left-lateralised regions associated with semantic processing, including fusiform, inferior parietal lobe and LIFG (Badre and Wagner, 2007; Binder et al., 2009).

2. Methods

2.1. Participants

Twenty-six right-handed adults aged 18-26 years underwent fMRI scanning. Data from one participant were lost due to data acquisition issues; a further five participants were excluded due to chance performance on the recognition test. Results for pattern separation and pattern completion analyses reflect data from the remaining 20 participants (M = 21.9 years; 10 female). For subsequent memory analyses, seven further participants were excluded due to insufficient false recognition trials (Section 2.7.1.). Subsequent memory analyses were therefore conducted on data from 13 participants (M = 21.8 years; 6 female). Informed consent was obtained, and the protocol received ethical approval. Subjective ratings of within-pair stimulus similarity were collected from a separate sample (Section 2.4.).

2.2. Materials

Stimuli were pairs of images (photographs or drawings, 300 x 270 pixels) of common objects or animals (Koutstaal, 2006). Pairs comprised perceptually similar exemplars of the same basic-level conceptual category, e.g., cats, telephones. Study phase lists contained 280 images: 200 novel, 40 repetitions of previously presented images, and 40 images which were perceptually and conceptually similar to previously presented images. Test lists comprised 240 images: 80 studied ('same') items, 80 lures of studied items ('similar') and 80 novel ('new') items. Lures presented at test had not been presented at study. Of the studied items presented at test, 20 had been presented twice at study (as novel then as a repetition), and for 20 of the 80 lures presented at test, corresponding items had been presented twice at study. Allocation of images to conditions was counterbalanced across participants. For study and test phases, a unique pseudo-random order of presentation was generated for each participant, with the constraint that no more than six items from one condition were presented in sequence. At the start of the scanned study phase, four 'filler' images were presented, and excluded from analyses.

2.3. Task and procedure

Stimuli were presented in Cogent2000 v1.29 (www.fil.ion.ucl.ac.uk) in MATLAB v.7.12 (The MathWorks Inc., 2011). The task comprised a scanned study phase and a subsequent recognition test, illustrated in Fig. 2. Stimuli were displayed through MRI-compatible Nordic Neurolab goggles (www.nordicneurolab.com) at an effective viewing distance of 1 m, and vision was corrected to normal if required. Images subtended approximately 10 degrees of visual angle. Earplugs were employed to reduce scanner noise, and head motion was minimised using foam pads. During the study phase, participants judged whether each depicted item would fit in a shoebox, responding 'yes' or 'no' via button presses on hand-held fibre-optic response pads. Images were presented centrally against a white background for 2200 ms, followed by a black fixation cross for 300 ms, then a red fixation cross for 300 ms (stimulus onset asynchrony (SOA) = 2800 ms). Novel images were separated from corresponding repetitions or similar images by 30 - 60 trials. Participants also viewed 40 fixation-only 'null' trials, in which the black fixation cross remained onscreen for the duration of one SOA.

Twenty-four hours after the study phase, participants completed a recognition test. Participants judged whether images presented were 'same', 'similar', or 'new' relative to studied items, or gave a 'guess' response. Responses were made via key presses. Images were presented for 3000 ms with a 1000 ms inter-trial interval (black fixation cross 700 ms, red fixation cross 300 ms; SOA = 4000 ms). Assignment of keys to responses was counterbalanced across participants. Practice sessions were conducted prior to study and test phases.

< Figure 2 about here>

2.4. Similarity ratings

Subjective similarity ratings were collected from a separate sample (N = 23; 18 – 25 years). The pairs of images employed in the main experiment were presented in sequence, with a unique pseudorandom order of presentation generated for each participant. Twelve participants rated the perceptual similarity of items within each pair from 1 (highly similar) to 5 (highly distinctive), and 11 rated intra-pair conceptual similarity on the same scale. Participants were asked to base perceptual similarity judgements on visual features such as shape or colour, and to base conceptual similarity judgements on how well the images corresponded to the same *kind* of object, i.e., two mountain bikes would be judged as conceptually similar, whereas a collie and bulldog, although both belonging to the basic-level category 'dog' should be rated less conceptually similar (Konkle et al., 2010). Image pairs were presented until 800 ms after a response was made, up to a maximum presentation time of 6000 ms. Between trials, a black fixation cross was presented for 1000 ms.

2.5. fMRI data acquisition

Images were acquired with a 1.5T Signa Horizon HDX MRI scanner operating under a research collaboration with GE Medical Systems (Milwaukee, USA). T2*-weighted functional images were acquired in a single session using a BOLD-EPI sequence (TR = 2200 ms, TE = 40 ms). Functional data consisted of 435 volumes, each comprising 30 slices (interleaved acquisition; 64 x 64 matrix; 4 mm x 4 mm x 4 mm). The first 4 volumes were discarded to account for T1 equilibration. Following functional scanning, T1-weighted structural images were obtained (fov = 24 cm; flip angle 8°, 256 x 256 matrix, 1mm x 1mm x 1.3 mm voxels).

2.6. Image preprocessing

MRI preprocessing and analysis were conducted in SPM8 (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB v.7.5 (The MathWorks Inc., 2007). Scans with slices showing average signal of greater than 7 standard deviations (*SD*) from the session mean were visually checked, and where artefacts were present scans were replaced with the average of the two adjacent scans (Foo et al., 1994) then modelled as confounds in the first level design matrix (see Section 2.7.1.). Functional images were corrected for temporal differences in slice acquisition using sinc interpolation in time, and spatially realigned to the mean EPI image using B-spline interpolation. For whole-brain analyses, spatial normalisation used the 'new segment' protocol in SPM8 (Ashburner and Friston, 2005): participants' structural scans were coregistered to their mean EPI image, then segmented into 6 tissue classes. Resulting parameters were applied to reslice the EPI images to 3 x 3 x 3 mm voxels in Montreal Neurological Institute (MNI) space. Finally, for the principal analyses the data were spatially smoothed with an 8 x 8 x 8 mm full-width half maximum Gaussian kernel.

2.7. fMRI data analysis

2.7.1. First and second level models and statistical thresholding

At the first level, vectors of onset times for each event type of interest for each participant were convolved with the canonical haemodynamic response function (HRF) and temporal derivative basis functions in a general linear model (GLM). Hypothesis testing involved construction of 5 separate first level models. Model i) implemented the overall pattern separation/completion analysis, and ii)-iv) the input similarity analyses. For the similarity analyses, model ii) identified repetition sensitive regions, then iii) modelled perceptual similarity and iv) conceptual similarity. Finally, v) modelled subsequent memory effects.

For the overall pattern separation and completion model (i), event types of interest were novel, repeated and similar items. Unlike previous fMRI studies, we defined pattern separation and completion within regions showing repetition enhancement as well as suppression. A difference in activity between novel and repeated items is necessary to reveal the relative responses to similar items, but both directions of repetition effect are consistent with computational definitions for pattern separation and completion. In ii), to define repetition sensitive regions the event types of interest were the novel and repeated items presented at study. For each participant, half of the novel items for which repeated or similar items were later presented, and half of the repeated items (40 and 20, respectively) were randomly selected to identify the repetition sensitive regions, and the remaining half were used for the similarity analyses iii) and iv). In ii), the 120 novel non-repeated items were also included to maximise sensitivity. For similarity analyses, stimulus pairs were divided into tertiles based on their average intra-pair perceptual (ii) and conceptual (iii) similarity ratings. Event types of interest were: novel items for which similar or repeated items were later presented; repetitions; similar items of high (S1); medium (S2); and low (S3) similarity; and null events. The novel and repeated items consisted of the half of the novel and repeated items (40 and 20) not included in the mode used to select repetition sensitive regions (ii). For model iii), for each class of similar item (S1, S2, S3), a continuous measure of perceptual similarity was included as a parametric modulator, convolved with the canonical HRF. Similarly, for model iv), continuous measures of conceptual similarity were included as parametric modulators for each of the similar conditions (S1, S2, S3). For models iii) and iv), novel items which were not subsequently repeated (either as similar items or repetitions) served as a non-fixation implicit baseline, following Motley and Kirwan (2012). For the subsequent memory model (v), encoding trials were sorted according to the response condition of corresponding studied/lure items at test. Event types of interest were hits to studied items (‘same’|studied), partial recognition of studied items (‘similar’|studied); lure false recognition (‘same’|lure); lure correct rejection (‘similar’|lure); and ‘forgetting’. For the latter event type, misses to both studied items and

lures ('new'|studied; 'new'|lure) were collapsed into a single category. Participants with fewer than 10 trials in any condition of interest were excluded from analyses.

For all models, the first two images presented during scanning and, for the subsequent memory model, trials receiving no response, were modelled as events of no interest. Regressors comprising a '1' in a column of zeroes representing removed scans were also included in the GLM as confounds, along with 12 motion parameters comprising the six rigid-body transformation outputs of the realignment stage, and the differences between these six parameters and the corresponding parameters of the previous scan (Friston et al., 1996). The time series was high-pass filtered using a cut-off of 128 s, and parameter estimates were computed using the weighted least squares model fitted to the data after prewhitening using an AR(1) plus white noise model (Friston et al., 2002).

For models i), ii) and v), fMRI data were analysed using a two stage summary statistic mixed-effects procedure (Penny and Holmes, 2006) (for iii and iv, group analyses were conducted on beta values extracted from first level models, Section 3.2.2.1.). *T*-contrasts for each event type (e.g., for pattern separation: novel, repetition, similar) against the implicit baseline were computed at the individual subject level and entered into one-way within-subjects analyses of variance (ANOVAs) at the group level, which modelled average subject effects and treated participants as random effects. GLMs were estimated using weighted least squares to account for non-sphericity (Friston et al., 2002). Main contrasts of interest employed one-tailed *t*-tests, producing statistical parametric maps of *t*-statistics at each voxel. Images for exclusive masking were computed using bidirectional *F*-tests. Correction for multiple comparisons employed AlphaSim's Monte Carlo permutation-based cluster threshold (Analysis for Functional NeuroImaging, afni.nimh.nih.gov; Cox, 1996). For a family-wise error (FWE) rate of $p < .05$, given a cluster-defining voxel threshold of $p < .01$, the cluster threshold was 67 contiguous voxels for whole-brain contrasts. Exclusive masks were applied at an uncorrected threshold of $p < .05$, to discount voxels from the resulting masked contrasts which showed any hint of the relevant masked effect. Results reported are for the canonical HRF.

2.7.2. Cortical region of interest (ROI) analyses

Pattern separation and subsequent memory effects were also examined in several *a priori* ROIs, listed in Table 1 along with a summary of the results of the analyses (see Section 3.2.). For each ROI, average beta values from first level models were extracted for event types of interest within spheres of 5 mm radius (3 mm in MTL) centred on peak coordinates from previous relevant studies. Differences in extracted beta values between events of interest were analysed using *t*-tests and ANOVA.

< TABLE 1 about here >

2.7.3. Hippocampal voxel-wise ROI analysis

In line with previous fMRI studies of pattern separation and pattern completion, targeted analyses were also conducted within the hippocampus using unsmoothed EPI data. To ensure optimal localisation and signal detection, the ROI-AL method of cross-participant alignment was used (Stark and Okado, 2003). Given the limited spatial resolution, both hippocampi together were treated as a single ROI. T1 structural scans were first normalised to MNI space in SPM8 using affine transforms, before hippocampal manual segmentation in ITK-SNAP (Boccardi et al., 2011; Yushkevich et al., 2006). Resulting segmentations were aligned using the Diffeomorphic Demons algorithm (Vercauteren et al., 2007) in MedINRIA (v1.8.0, ASCLEPIOS Research Team, France) to a hippocampal mask derived from manual segmentation of the T1 canonical brain. Segmentations were then realigned to a template derived from the mean of the post-aligned ROIs from the previous step. The displacement fields generated were applied to participants' preprocessed EPI time series, and first and second level models re-estimated (Section 2.7.1.). Voxel-wise analyses were conducted within the group hippocampal mask. For a FWE of $p < .05$ given a cluster-defining voxel threshold of $p < .01$, a cluster threshold of 3 voxels was determined using AlphaSim.

2.7.4. Functional overlap

We tested for joint significance of the conjunction of each pattern separation or completion contrast with each item-specific or gist encoding contrast which revealed significant findings. A conjoint voxel threshold was applied following inclusive masking of each encoding contrast with the relevant pattern separation/completion contrast. With the individual contrasts thresholded at the original significance level of $p < 0.01$, the conjoint uncorrected voxel significance level was $p < .001$ according to Fisher's formula (Fisher, 1950; Lazar et al., 2002). Using AlphaSim, the cluster threshold for FWE correction at $p < .05$ given this conjoint voxel significance level was 20 contiguous voxels.

3. Results

3.1. Behavioural results

3.1.1. Study phase

One-way ANOVA examining mean reaction time (RT) at study showed that responses on the size judgement task were faster to repetitions (830 ms) and similar items (863 ms) compared to novel items (953 ms; $F(2,38) = 38.4$; $t(19) = 8.06$; $t(19) = 6.52$; all $p < .001$). No differences were observed in RT at study according to memory response at test ($F < 1$). As the size judgement task contained a subjective element, accuracy was not assessed.

3.1.2. Test phase

Analyses of test phase memory accuracy and RTs were conducted on data from the 13 participants included in subsequent memory analyses. RT at test differed according to the Condition of items (studied, repetition, lure; $F(2,24) = 14.31$, $p < .001$) and the Response given ('same', 'similar', 'new'; $F(2,24) = 7.24$, $p = .003$). A Condition x Response interaction ($F(4,48) = 7.15$, $p < .001$) was followed up via *t*-tests contrasting correct with incorrect responses separately for each Condition. For studied items, correct 'same' responses were faster than incorrect responses ('similar': $t(12) = 4.72$, $p = .001$; 'new': $t(12) = 2.18$, $p = .05$). Novel items were correctly identified as 'new' faster than they were incorrectly judged 'same' or 'similar' ($t(12) = 2.35$, $p = .037$; $t(12) = 3.21$, $p = .007$). Participants were slower to correctly reject lures than to falsely recognise lures as 'same' ($t(12) = 2.25$, $p = .04$), and no difference in RT was observed between correct 'similar' and incorrect 'new' responses to lures ($t(12) = 1.96$, $p = .07$).

Proportions of responses associated with each Condition (studied, lure, novel) at test were computed for the 13 participants included in subsequent memory analyses (see Fig. 3). Three one-way ANOVAs examined effects of Condition (studied, lure, novel) separately for each Response ('same', 'similar', 'new'). Effects of Condition were present for each Response ('same': $F(2,24) = 234.83$, $p < .001$; 'similar': $F(2,24) = 27.22$, $p < .001$; 'new': $F(1.2,14.7) = 71.0$, $p < .001$). *Post hoc* tests for each Response type (adjusted $\alpha = .017$) revealed that correct 'same' responses to studied items were more frequent than false recognition of lures or novel items ($t(12) = 15.17$; $t(12) = 16.82$; ps $< .001$), and lures were falsely recognised more often than novel items ($t(12) = 9.48$, $p < .001$). 'Similar' responses were assigned to lures more often than studied or novel items ($t(12) = 8.13$; $t(12) = 5.25$; ps $< .001$), but there was no difference in the proportions of studied and novel items judged 'similar' ($t(12) = .58$, $p = .58$). Novel items were judged 'new' more often than studied items or lures ($t(12) = 8.85$; $t(12) = 8.02$; ps $< .001$), and studied items received fewer 'new' responses than lures ($t(12) = 7.02$, $p < .001$).

< Figure 3 about here >

3.1.3. Similarity ratings

The average perceptual similarity rating of image pairs was 2.89 ($SD = .68$, range 1.33 - 4.58) and the average intra-pair conceptual rating was 3.01 ($SD = .63$, range 1.64 - 4.45). Conceptual and perceptual ratings were positively correlated across items ($r = .64$, n = 280, $p < .001$).

3.2. fMRI results

3.2.1. Pattern separation and pattern completion

3.2.1.1. Analysis strategy

To assess pattern separation, we searched for regions in which average activity elicited by novel and similar items was greater than activity for repetitions (repetition < similar = novel), using a one-tailed *t*-contrast at the group-level. To discount regions showing any hint of differential activity between novel and similar items, the resulting SPM was exclusively masked with the bidirectional *F*-contrast of novel vs. similar (Section 2.7.1.). To detect pattern separation activity in regions showing greater activity for repetitions than novel items, a 'reverse' pattern separation contrast was computed (repetition > similar = novel), again exclusively masked with the *F*-contrast of novel vs. similar. For pattern completion, *t*-contrasts located regions in which activity elicited by novel items was greater than that for both similar items and repetitions (repetition = similar < novel), exclusively masked with the *F*-contrast of similar vs. repeated items. A 'reverse' pattern completion contrast also examined regions showing increased activity to similar and repeated relative to novel items (repetition = similar > novel).

3.2.1.2. Findings

Regions showing suprathreshold pattern separation and completion-consistent activity in the whole brain analysis are summarised in Table 2 and selected regions are illustrated in Fig. 4 (pattern separation) and Fig. 5 (pattern completion). Pattern separation (repetition < similar = novel) activity was observed in bilateral PFC and occipito-temporal regions including a lateral prefrontal region encompassing LIFG (BA 46) and left middle frontal gyrus (LMFG; BA 9), and right inferior frontal gyrus (RIFG; BA 9), right inferior temporal cortex and left middle temporal gyrus. Reverse pattern separation activity (repetition > similar = novel) was observed in right inferior parietal cortex. Pattern completion activity (repetition = similar < novel) was revealed in a region of LIFG (BA 46/47) which overlapped but was slightly more anterior to that revealed in pattern separation contrasts. The 'reverse' pattern completion contrast (repetition = similar > novel) revealed activity in left superior frontal and left supramarginal gyri, and right precuneus.

The *a priori* ROI analyses (Table 1) revealed activity consistent with pattern separation in right fusiform, bilateral middle occipital cortex, and posterior LIFG (BA 44). Voxel-wise ROI analysis in hippocampus showed pattern completion activity in a left anterior region (Table 3).

< TABLE 2 about here>

< FIGURE 4 about here >

< FIGURE 5 about here>

<TABLE 3 about here >

3.2.2. Input similarity

3.2.2.1. Analysis strategy

To ensure independence of input similarity analyses from the ROI selection procedure, repetition sensitive regions were first identified by conducting unidirectional *t*-contrasts of novel > repeated, and repeated > novel using half of the items in each of these conditions (Section 2.7.1. for model and thresholding; Table 4 for results). Voxel-wise ROI analysis in the hippocampus did not reveal any repetition sensitive regions which survived thresholding, so model fit was examined in cortical repetition sensitive regions (Table 4) and *a priori* ROIs (Table 1) only. Input similarity analyses were conducted using the remaining half of the novel and repeated items within ROIs centred on the peak voxels of all regions which showed significant differences between novel and repeated items, and for the *a priori* ROIs for which pattern separation was supported in whole-brain analyses (Section 3.2.1.2.). Next, beta values extracted from first level models for each ROI were averaged across participants for each trial type – repetitions, high (S1), medium (S2), and low (S3) similarity items, and first presentations of novel items. Using the Curve Fitting Toolbox (v3.4) in MATLAB (v8.2), linear ($f(x) = ax + b$) and power functions ($f(x) = ax^b + c$) were fitted to the data for each ROI, with each data point weighted by the inverse of the square of the standard error (Machluf, 2008). Power functions with decreasing slope are defined as functions where b (the exponent) < 0, and increasing slope power functions where $b > 1$ (Motley & Kirwan, 2012). The least squares analogue of Akaike's Information Criterion, including correction for small sample size (AIC_c) was calculated using: $AIC_c = n\log(SSE/n) + 2K + (2K(K+1))/(n-K-1)$, where n is the sample size, SSE is the sum of squared error, and K is the number of model parameters, including the error term (Burnham and Anderson, 1998). For each similarity measure, comparative fit of each linear and power model was assessed via AIC_c, adopting the criterion that a difference in AIC_c of greater than 4 corresponds to significant evidence of a difference in model fit (Burnham and Anderson, 1998), with better fit for the model with the lower AIC_c value. To avoid formal comparison of very poor fitting models, model fit was compared using AIC_c only where adjusted $R^2 > 0$ (indicating the model provides better fit than a horizontal line) for one or both models.

For five out of six repetition sensitive regions, the peak voxel coordinates fell within a pattern separation or completion cluster revealed in the whole-brain contrasts (Section 3.2.1.2.). Findings of the curve fitting analysis were therefore interpreted in light of this overlap, to determine whether fitted curves were consistent with the overall analysis. The predicted function for pattern separation in regions showing repetition suppression (including *a priori* ROIs) was a power function with

decreasing slope (above the diagonal in Fig. 1A) for responses to repetitions, items of high, medium and low similarity, and novel items, The predicted function for pattern completion was a power function with increasing slope. Using a stricter operationalisation of pattern completion than Motley and Kirwan (2012), who also interpreted linear functions as evidence of pattern completion, we classified a linear function as consistent with neither pattern separation nor completion (see Introduction). In regions showing repetition enhancement, the direction of response functions consistent with pattern separation and completion was reversed: pattern separation is expected to approximate the decreasing slope power function below the diagonal in Fig. 1B, and pattern completion the increasing slope power function above the diagonal.

<TABLE 4 about here>

3.2.2.2. Findings

Repetition sensitive regions are summarised in Table 4. Model fit is summarised in Table 5, and full model parameters are listed in Supplementary Table S1. Best fitting curves for ROIs showing model fit consistent with pattern separation are depicted in Fig. 6. The RIFG cluster overlapped with an RIFG cluster revealed in the whole-brain pattern separation contrast (repetition < similar = novel) and showed decreasing slope power functions for both conceptual and perceptual similarity, consistent with pattern separation. AIC_c differences between the power and linear models were 13.33 and 14.46 for conceptual and perceptual similarity, respectively, and for both similarity measures, linear models showed very poor fit (adjusted $R^2 < 0$), suggesting better fit for the power function. The right superior temporal gyrus cluster overlapped with a right inferior parietal reverse pattern separation cluster (repetition > similar = novel) but did not show sufficiently reduced AIC_c for the best fitting decreasing slope power function for conceptual similarity relative to the linear function (AIC_c difference = 1.56). However, the right supramarginal gyrus subpeak of this cluster was closer to the peak of the overlapping right inferior parietal cluster (4.2 vs.14.7 mm; see Table 4) and showed better fit for the decreasing slope power model for conceptual similarity, consistent with pattern separation (AIC_c difference = 19.41).

Among the *a priori* ROIs, posterior LIFG showed the predicted power function with decreasing slope for conceptual similarity, indicative of pattern separation and consistent with the overall analysis (AIC_c difference =8.59). Contrary to predictions however, the right middle occipital (RMO) ROI showed best fitting *increasing* slope power functions for both conceptual and perceptual similarity (AIC_c differences = 29.42 and 18.31). For all other ROIs, including a left anterior cingulate region which did not overlap with pattern separation or completion regions, support for the predicted pattern separation or completion function was not found.

< TABLE 5 about here >

< FIGURE 6 about here >

3.2.3. Subsequent memory

3.2.3.1. Analysis strategy

Encoding trials were sorted according to responses in the subsequent recognition test (see Fig. 3). Subsequent hits to studied items and subsequent correct rejection of lures were classified as item-specific memory, while subsequent partial recognition of studied items as 'similar' and subsequent false recognition of lures as ‘same’ were classified as gist memory (Garoff et al., 2005). Misses (‘new’ responses) of studied items and lures comprised the subsequent forgetting category. Hits versus partial recognition of studied items, and correct rejection versus false recognition of lures were analysed as two distinct subsequent memory effects, one relating to encoding supporting recognition of studied items, the other to encoding supporting mnemonic discrimination of lures (Cheng and Rugg, 2010). To examine encoding predicting gist memory, we used unidirectional *t*-contrasts to identify activity increases for subsequent partial recognition relative to subsequent hits; and for subsequent false recognition relative to subsequent lure correct rejection. As both partial and false recognition have been proposed to reflect gist memory (Garoff et al., 2005), to maximise trials available for gist contrasts and to allow comparison with the results of Garoff et al. (2005), additional contrasts also collapsed subsequent partial and false recognition into a single 'gist memory' category, and compared this separately with subsequent hits and subsequent correct rejection. The reverse contrasts were also computed (subsequent hits > subsequent partial recognition; subsequent correct rejection > subsequent false recognition, and each item-specific memory outcome > subsequent gist memory). Finally, each response category was also contrasted with subsequent forgetting.

3.2.3.2. Findings

Results of the subsequent memory analyses are summarised in Table 6. Encoding of items attracting subsequent hits, when compared with subsequent gist memory (partial recognition of studied items and false recognition of lures) elicited greater activity in right superior temporal gyrus, posterior LIFG, and left middle occipital gyrus. The contrast of subsequent hits vs. subsequent partial recognition revealed activity in right precuneus and left middle occipital gyrus. Encoding predicting lure correct rejection compared to lure false recognition elicited greater activity in posterior cingulate. Encoding predicting subsequent gist memory, when contrasted with encoding predicting subsequent lure correct rejection, revealed activity in left inferior parietal lobe.

< TABLE 6 about here >

The voxel-wise analysis in the hippocampus showed that activity in right posterior and left anterior regions predicted subsequent correct rejection of lures relative to subsequent gist memory (Table 3). Activity in a left posterior region was also greater for encoding of items for which lures were subsequently falsely recognised compared to items for which lures were correctly rejected.

3.2.4. Overlap between pattern separation/completion and item-specific/gist encoding

3.2.4.1. Analysis strategy

Functional overlap between pattern separation or pattern completion and mnemonic encoding was assessed by searching for regions showing conjoint activity between significant contrasts employed in pattern separation and subsequent memory contrasts (see Sections 2.7.1., 3.2.1.1. & 3.2.3.1. for masking and thresholding procedures) for the 13 participants included in both analyses.

3.2.4.2. Findings

The conjoint analysis revealed significant functional overlap between regions engaged in pattern separation and encoding predicting hits to studied items (Table 7 & Fig. 7). Bilateral inferior frontal and left middle occipital regions showed both pattern separation (repetition < similar = novel) and greater activity for subsequent hits than subsequent gist memory. Overlap was also observed between pattern separation activity and encoding activity predicting subsequent hits relative to subsequent partial recognition in left occipital and right inferior frontal cortex. No significant functional overlap was observed between pattern separation and gist encoding, or between pattern completion and either item-specific or gist encoding.

< TABLE 7 about here >

< FIGURE 7 about here >

4. Discussion

This is the first study to investigate cortical pattern separation and completion of visual object representations in humans. We found neural activity consistent with pattern separation in occipito-temporal cortex and bilateral lateral PFC, and pattern completion in left anterior PFC and right precuneus. In bilateral lateral PFC, and right parietal regions, responses to parametrically varied conceptual and perceptual input similarity provided further evidence for pattern separation. The data

603 are in line with computational predictions (Treves and Rolls, 1992; Vazdarjanova and Guzowski,
604 2004) and with findings of pattern separation and completion computations in sensory cortex in
605 rodents (Aimone et al., 2011; Barnes et al., 2008). Bilateral prefrontal and left occipital cortex regions
606 showing pattern separation activity were also engaged during encoding predicting subsequent true
607 recognition, consistent with suggestions that cortical pattern separation contributes to successful item-
608 specific encoding. Contrary to predictions, we did not detect overlap between pattern separation
609 activity and encoding activity associated with later mnemonic discrimination of lures, although
610 activity in the hippocampus did predict accurate lure rejection, in line with previous findings (e.g.,
611 Kirwan & Stark, 2007). The data are consistent with the view that cortical pattern separation at
612 encoding contributes to successful item-specific memory, but that further processes, such as encoding
613 of gist and item-specific information, contribute to later mnemonic outcomes.
614

615 **4.1. Behavioural findings**

616 Reaction time data did not reveal any evidence that later recognition outcomes were due to
617 differences in duration of processing at study. Faster RTs at study to both repeated and similar items
618 are consistent with priming of similar items based on overlapping perceptual or conceptual features
619 (Stenberg et al., 2009). Performance on the 'same/similar/new' recognition test was similar to that in
620 previous reports (Garoff et al., 2005; Stark et al., 2013; Toner et al., 2009) with participants most
621 often correctly classifying studied, lure and novel images as 'same', 'similar' and 'new', respectively.
622 Proportions of 'similar' responses to each item type were lower than in Garoff et al.'s (2005) earlier
623 study which employed the same retention interval and largely the same stimulus set. This may be
624 explained by the fact that in Garoff et al.'s (2005) study, a higher proportion of test items were lures
625 (2/5) compared to the current study (1/3), which may have led to greater bias to respond 'similar' in
626 the original study. This may also be why responses here but not in the previous study were also less
627 accurate for lures than for studied and novel items. The pattern observed here is consistent with
628 previous findings of reduced performance for lures (e.g., Stark et al., 2013; Toner et al., 2009), and
629 with claims that lure discrimination places greater demands on pattern separation (Kirwan and Stark,
630 2007; Yassa et al., 2011) and/or post-retrieval processing (Brainerd et al., 2003; Morcom, 2015) and
631 is therefore associated with reduced accuracy.
632

633 **4.2. Pattern separation and pattern completion**

634 As predicted, contrasts of study phase activity elicited by novel, repeated and all similar items
635 revealed evidence of pattern separation in bilateral occipito-temporal cortex in both *a priori* and
636 whole-brain analyses. This is consistent with neurophysiological evidence of orthogonalisation of
637 input in sensory cortex (Barnes et al., 2008; Wilson, 2009). These findings extend those of fMRA

studies reporting sensitivity of visual regions to subtle perceptual change in images (Chouinard et al., 2008; Kim et al., 2009; Koutstaal et al., 2001), by identifying occipito-temporal clusters of activity that show differential activity between repetitions and both novel and similar items, with no hint of activity differences between novel and similar items. Curve fitting analysis did not however provide additional support for true computational pattern separation in occipito-temporal regions.

We also observed activity consistent with pattern separation in bilateral, mainly posterior and inferior, regions of lateral frontal cortex. In bilateral inferior frontal and right parietal areas, converging evidence from the overall analyses and from curve fitting supported pattern separation, indicative of sensitivity to item novelty despite overlapping representations. The prefrontal regions have been linked to cognitive control functions including selection among competing memory representations (Badre and Wagner, 2007; Dudukovic and Wagner, 2007), and goal-related attentional modulation of sensory signals in extrastriate visual regions (Zanto et al., 2011), and of hippocampal processing (Summerfield et al., 2006). Such top-down modulation is consistent with other evidence that the regions engaged in pattern separation or completion vary according to the orienting task as well as the stimuli (Hashimoto et al., 2012; Motley and Kirwan, 2012). Parametric analysis indicated both conceptual and perceptual pattern separation in the right inferior frontal region. A contribution of both similarity dimensions is in keeping with the task goals which made both dimensions of individual items relevant. However a dominance of conceptual separation in the posterior LIFG ROI may also reflect its proposed specialisation for resolution of competition between active semantic representations (Badre et al., 2005; Thompson-Schill et al., 1999). The present data raise the possibility that pattern separation computations may contribute to this resolution.

Suggestions of pattern completion from initial contrasts in regions including anterior inferior left PFC, right precuneus and left parietal lobe were not borne out by the more specific parametric similarity analysis. In the case of the left prefrontal regions, lack of significant repetition sensitivity when only the subset of novel and repeated items were analysed precluded examination of input response functions. Other repetition sensitive ROIs did overlap with clusters revealed in the overall pattern separation (e.g., left and right middle occipital, right inferior occipital) or completion (left inferior parietal, right precuneus) contrasts, but did not show the predicted model fit for these computations. Selection of repetition sensitive ROIs using different trials from those included in similarity analyses allowed us to ensure that the two pattern separation/completion analyses were independent, but this reduced the number of trials in both analyses. Although this presumably impacted sensitivity, the only inconsistent result between the two was in the right middle occipital *a priori* ROI, in which the two analyses showed repetition effects of opposite direction. No region showed greater evidence for a linear response than for the increasing/decreasing slope power functions predicted for pattern separation or completion in the closest or overlapping peak. Future studies examining response functions in *a priori* ROIs centred on the pattern separation and

674 completion regions revealed in the present overall analyses may observe supporting evidence of these
675 processes.
676 We did not find clear-cut evidence for either hippocampal pattern separation or completion,
677 despite previous findings (e.g., Bakker et al., 2008; O'Reilly and McClelland, 1994). The lower
678 spatial resolution here compared to previous fMRI studies of hippocampal pattern separation (Bakker
679 et al., 2008; Yassa et al., 2011) is the most likely explanation, as the current data did not permit
680 anatomical separation of responses in the hippocampal subregions in which pattern separation (DG)
681 and completion (CA1) signals have previously been reported (e.g., Hunsaker and Kesner, 2013;
682 Leutgeb et al., 2007).
683

684 **4.3 Item-specific and gist encoding**

685 Regions active at encoding differed according to whether subsequent memory was item-
686 specific, i.e., accurate recognition of studied items or mnemonic discrimination of lures; or gist-based,
687 i.e., false recognition of lures or partial recognition of studied items. Occipito-temporal regions
688 including left middle occipital cortex showed greater activity for encoding supporting accurate
689 recognition as opposed to gist memory, consistent with reports that visual processing supports later
690 item-specific memory for visually presented stimuli (Baym and Gonsalves, 2010; Kim and Cabeza,
691 2007; Kim, 2011). Posterior LIFG was also found to be engaged in encoding predicting accurate
692 recognition, consistent with Kim's (2011) meta-analysis of 74 subsequent memory studies.
693 We provide the first fMRI examination of encoding activity specific to subsequent mnemonic
694 discrimination of lures. Garoff et al. (2005) used the same retrieval task, but assumed that 'similar'
695 responses to lures may rely on either specific or gist memory, and so did not examine encoding linked
696 specifically to this response category. However, others have argued that mnemonic discrimination of
697 lures depends more than accurate recognition on item-specific encoding (Tun et al., 1998; see
698 Introduction). Only one cortical region was associated with subsequent lure discrimination, in left
699 posterior cingulate gyrus. The paucity of cortical responses observed to predict mnemonic
700 discrimination may reflect some lack of sensitivity, but it is also possible that this recognition
701 outcome in fact depends more on retrieval than on encoding processing, or relies more heavily on
702 hippocampal encoding processes, such as pattern separation, than cortical encoding (Yassa and Stark,
703 2011). Indeed, right posterior and left anterior hippocampus showed greater activity during encoding
704 predicting later mnemonic discrimination compared to later gist memory, supporting a critical role for
705 this region in mnemonic discrimination.
706 Left inferior parietal cortex and left posterior hippocampus showed greater activity during
707 encoding predicting later gist memory compared to lure correct rejection. Garoff et al. (2005)
708 identified a similar left inferior parietal region using similar contrasts, and proposed that activity in
709 this and other bilateral frontal and parietal regions reflected elaborative processing of semantic

information at encoding, contributing to subsequent reliance on gist information (Buckner et al., 1998). The cluster in left posterior hippocampus is also close to a region previously linked to subsequent recollection of gist (Manelis et al., 2013), supporting assumptions that false recognition is often driven by overlapping gist (Brainerd and Reyna, 2002).

Fewer regions were associated with gist encoding here than in Garoff et al.'s (2005) investigation, in which multiple bilateral cortical regions showed activity increases for gist encoding compared to both item-specific encoding and subsequent forgetting. A notable difference between the two studies is that Garoff et al. (2005) examined only encoding trials associated with later recognition responses which were rated as highly confident, whereas here, all encoding trials associated with a later 'same/similar/new' response were included in analyses. Garoff et al.'s (2005) wider cortical engagement in gist encoding may reflect this difference. Alternatively, the greater rate of partial recognition of studied items in Garoff et al.'s (2005) study (see Section 4.1.) may have meant that their findings for gist encoding reflected forgetting to a greater degree than in the present study.

4.4. Pattern separation/ completion and encoding

Bilateral inferior frontal cortex and left middle occipital cortex were found to be active in conjoint contrasts of pattern separation and encoding predicting subsequent hits (Table 7). In RIFG, curve fitting analysis provided further support for conceptual and perceptual pattern separation. These findings are consistent with the suggestion that cortical pattern separation at encoding contributes to accurate recognition memory (e.g., Sahay et al., 2011; Schacter et al., 1998; Stark et al., 2013 Wilson et al., 2006). The assignment of unique neural representations to novel input (pattern separation) may aid formation of item-specific memory traces which later enable successful recognition of studied items (Kirwan and Stark, 2007). Regions in the ventral visual stream are thought to represent object features at increasing levels of complexity (Cowell et al., 2010a), and lesion data suggest that these representations contribute to recognition memory (Cowell et al., 2010b; Norman and Eacott, 2004). According to this hierarchical view, the occipital region showing functional overlap may contribute to encoding of unique visual representations via pattern separation. Pattern separation occurring in the ventral visual processing stream might influence the degree of pattern separation occurring within the hippocampus and thus impact on recognition outcomes, or may contribute independently to recognition (Cowell et al., 2010b; Yassa and Stark, 2011). The data are likewise consistent with the notion that pattern separation in bilateral inferior PFC supports later recognition. One possibility is that the resolution of interference between overlapping representations may contribute to item-specific encoding. However while the functional overlap we observe goes beyond existing data in supporting the proposed contribution of pattern separation to successful encoding, further, more direct evidence is required to provide more robust support. This is particularly true in occipital cortex, in which there was no converging evidence of pattern separation from the input similarity analyses. First, as

discussed in Section 4.2., more sensitive assessment of input similarity response functions in these regions of overlap is needed in independent samples. Second, demonstration of stronger pattern separation effects at encoding for items which are later correctly recognised compared to those which are later forgotten would provide a clearer indication that the strength of pattern separation contributes to these subsequent memory outcomes. Limited trial numbers and the fact that similar items presented at study were not repeated at test meant this could not be assessed in the current study, but these are important directions for future investigations.

Contrary to our predictions, encoding activity predicting subsequent lure mnemonic discrimination did not engage any cortical regions which also showed evidence of pattern separation. As noted above, mnemonic discrimination may rely to a greater extent on hippocampal pattern separation at encoding than on cortical pattern separation. As we did not detect hippocampal pattern separation, overlap with later mnemonic discrimination could not be directly assessed. A critical role of the hippocampus in encoding supporting later mnemonic discrimination is however suggested by neuropsychological and ageing studies (e.g., McHugh et al., 2007; Yassa et al., 2010), and is consistent with our findings of hippocampal engagement in encoding predicting lure discrimination. It is possible that the occipital and PFC regions identified here as involved in pattern separation contribute to representing items uniquely, avoiding catastrophic interference in memory and enabling later recognition. However, it is likely that further processing performed on the hippocampus' multi-dimensional and contextual representations (Cowell et al., 2010a; Ranganath, 2010) also critically influences later explicit mnemonic discrimination of similar lures.

4.5. Limitations and future directions

The current study provides the first evidence in humans of computational pattern separation and pattern completion in cortical regions, the data are consistent with the view that cortical pattern separation contributes to memory encoding. However while the overall analysis comparing activity for similar items with that for repeated and novel items revealed activity consistent with the computational properties of pattern separation or completion (Kumaran and Maguire, 2009), it remains possible that it reflects other memory-related processes. Even in an incidental task, some explicit recognition may have been triggered by repeated and similar items at study, and it is possible that novel, similar and repeated items systematically differed in the degree of elaborative encoding elicited. . The prefrontal regions revealed in the pattern separation contrasts have been implicated in episodic retrieval (see Kim, 2013 for meta-analysis), as well as in semantic elaboration at encoding (Dobbins et al., 2002; Han et al., 2012). However, both accounts would predict lure responses intermediate in magnitude between responses to novel items and repetitions. Retrieval of the study episode would presumably be triggered most frequently by repetitions, less frequently by lures, and less again by novel items. It is also likely novel items would elicit the greatest semantic elaboration,

and repeated items the least. The pattern separation account on the other hand uniquely predicts that on average, similar items show equivalent activity to novel items (or repeated items in the case of pattern completion), and makes specific computational predictions relating to response functions to parametrically varied input similarity. In parametric analyses, there was little evidence of the linear pattern which would be expected if the encoding data were explained by a retrieval or elaborative encoding account. A further possibility is that the responses in regions revealed in pattern separation and completion contrasts reflect relative novelty or familiarity. However this too would predict a linear response (Carr et al., 2010), and is therefore inconsistent with our findings.

In line with previous definitions of pattern separation, we operationalized these processes in terms of the equivalence and difference of their neural responses to repeated, similar and novel (e.g., Bakker et al., 2008). However, unlike previous studies our analysis was unconstrained by the direction of the repetition suppression or enhancement effect, rather than limited to regions showing repetition suppression (e.g., Bakker et al., 2008; Lacy et al., 2011). Our inclusion of regions showing repetition enhancement was exploratory, but in some cases – just as for regions showing repetition suppression – was supported by findings of the predicted parametric response functions. It would be of interest to determine whether future high resolution fMRI studies show this pattern of activity within the hippocampal subregions known to be associated with pattern separation and completion.

Because of the nature of the BOLD signal, the parametric fMRI analyses can provide only relatively indirect measures of pattern separation and completion compared to direct neuronal recordings (Hunsaker and Kesner, 2013). Converging evidence of these processes in human studies could also be provided by representational similarity analysis (Kriegeskorte et al., 2008). Given *a priori* data regarding connectivity, representational similarity of novel and similar items could be compared between pattern separation/ completion regions and their input regions. Evidence of reduced representational similarity for a region relative to its input region would support the presence of pattern separation, while increased representational similarity would support pattern completion.

The present data are consistent with the notion that cortical pattern separation contributes to successful encoding. However, the fact that several regions showed cortical encoding-related activity which predicted item-specific outcomes but did not show evidence of pattern separation or completion – although these are null results – suggests that encoding mechanisms other than pattern separation also contribute to recognition memory. This is as expected based on the fuzzy-trace theory view that recognition failure reflects reliance on gist traces, formed as a result of semantic overlap between studied episodes (Brainerd and Reyna, 2002). In principle, the fuzzy trace account is compatible with a critical role for cortical pattern separation in reducing semantic overlap at the time of encoding (Winocur et al., 2010; Wilson et al., 2006; Yassa and Reagh, 2013; see also Pidgeon and Morcom, 2014), but in the current study, we did not find clear evidence for such a role. Although one region in RIFG showed both conceptual pattern separation responses and item-specific encoding activity, it also showed perceptual pattern separation responses. However, we were not able to assess perceptual and

conceptual pattern separation systematically in regions overlapping with the encoding-related contrast, since these were not revealed in the repetition sensitivity contrasts. In other regions a stronger tendency for reduction of conceptual relative to perceptual similarity was hinted at in the curve fitting analyses: right parietal and left inferior frontal regions showed activity consistent with conceptual but not perceptual pattern separation, and no regions showed evidence of perceptual pattern separation alone. Future studies can more directly assess this proposal by examining the specific relation between semantic similarity and the success of later mnemonic discrimination in the regions implicated here in both pattern separation and specific memory encoding.

4.6. Conclusions

Our data suggest that pattern separation and pattern completion of perceptually and conceptually similar object representations extends beyond the hippocampus to prefrontal and occipito-temporal regions, supporting claims that these processes occur throughout the brain (Aimone et al., 2011; Barnes et al., 2008). By examining neural response to images varied in their similarity relative to previously viewed images, we provide evidence that the neural responses in several regions met computational predictions for pattern separation or completion for either or both perceptual and conceptual similarity. The further finding that some regions showed activity consistent with both pattern separation and item-specific encoding is consistent with the notion that these computations in cortex contribute to episodic memory.

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Figure captions

Fig. 1. Predicted input-output response functions for pattern separation and pattern completion regions. S1 = high similarity items, S2 = medium similarity items, S3 = low similarity items. **A)** In regions showing repetition suppression, pattern separation is predicted to show a power function with decreasing slope in response to change in input, falling above the diagonal. Pattern completion regions are expected to fit an increasing slope power function, falling below the diagonal. **B)** In regions where repetitions show increased activity relative to novel items, functions in the opposite direction are predicted. Pattern separation is predicted to show a decreasing slope power function falling below the diagonal, and pattern completion an increasing slope power function falling above the diagonal. In **A)** and **B)**, the linear diagonal represents cases where change in input and change in output are equal. Adapted from Motley & Kirwan (2012).

Fig. 2. Experimental procedure. At study, participants performed a size judgement task, judging whether each item would fit in a shoe box. Novel images, repetitions, and similar images were presented. At test, participants responded 'same', 'similar', 'new' or 'guess' to studied, lure and novel items (see Section 2.3. for details).

Fig. 3. Proportions of 'same', 'similar' and 'new' responses to studied, lure and novel items during the recognition test. Means ± SE.

Fig. 4. **Pattern separation in selected cortical regions.** A) Pattern separation (repetition < similar = novel) in right inferior temporal gyrus (peak [39, -61, -8]) and B) 'reverse' pattern separation (repetition > similar = novel) in right inferior parietal lobule (peak [50, -46, 28]). In bar plots, y-axes represent parameter estimates (arbitrary units). The plots show activity change (arbitrary units) ± SE in these regions to repeated (R), all similar (S) and novel (N) items relative to fixation at peak voxels of clusters revealed in whole-brain pattern separation contrasts (see Sections 2.7.1. and 3.2.1.1. for thresholding and analysis). Sections show activity superimposed on the SPM8 canonical T1 image.

Fig. 5. **Pattern completion in selected cortical regions.** A) Pattern completion activity (repetition = similar < novel) in left inferior frontal gyrus (peak [-48, 31, 8]) and B) 'reverse' pattern completion (repetition = similar > novel) in left superior frontal gyrus (peak [-24, 57, 1]). In bar plots, y-axes represent parameter estimates (arbitrary units). Plots show activity change (arbitrary units) ± SE in these regions to repeated (R), all similar (S) and novel (N) items relative to fixation at peak voxels of clusters revealed in whole-brain pattern separation contrasts (see Sections 2.7.1. and 3.2.1.1. for thresholding and analysis). Sections show activity superimposed on the SPM8 canonical T1 image.

Fig. 6. Best fitting curves for perceptual (blue) and conceptual (red) similarity in repetition sensitive (A-B) or a priori (C) ROIs. Data points reflect activity to repetitions (R), items of high (S1), medium (S2) and low (S3) perceptual or conceptual similarity (relative to previously viewed images), and 1st presentations of novel items (N). (A) RIFG (51, 8, 25), revealed in the novel > repeated contrast, showed the predicted decreasing slope power functions for both similarity measures, consistent with pattern separation. (B) R supramarginal gyrus (51, -52, 25) showed the predicted decreasing slope power function for conceptual similarity only, consistent with pattern separation. (C) The a priori posterior LIFG ROI (-37, 2, 31) showed the predicted decreasing slope power function for conceptual similarity only. Mean beta values ± SE. Model fit parameters are summarised in Table 5 and Table S1.

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Fig. 7. **Regions showing functional overlap between pattern separation and item-specific encoding.** Sections show activity superimposed on the SPM8 canonical T1 image. In bar plots, y-axes represent parameter estimates (arbitrary units). Plots of parameter estimates provide a visual illustration of the pattern of responses observed in these regions, but are not intended to contribute to any inference within these regions. (A) Plots show mean parameter estimates (arbitrary units) ± SE for conditions of interest in repetition < similar = novel (top row) and Hits > Gist (PR and FR; bottom row) contrasts (compared to baseline) in peak voxel of left inferior frontal cortex region [-45, 11, 22]. (B) Plots show mean parameter estimates (arbitrary units) for conditions of interest in repetition < similar = novel (top row) and Hits > PR of Studied items (bottom row) contrasts in peak voxel of left occipital region [-30, -88, -2]. See Section 3.2.4.1. for analysis strategy.

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